UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/464,303 | 12/15/1999 | GREGORY L. STAHL | B0801/7156 | 7348 |

7590 03/01/2005

HELEN C LOCKHART
WOLF GREENFIELD & SACKS P C
600 ATLANTIC AVENUE
BOSTON, MA 02210

| EXAMINER | |
|---|---|
| VANDERVEGT, FRANCOIS P | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | |

DATE MAILED: 03/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/464,303 | STAHL ET AL. | |
| | Examiner | Art Unit | |
| | F. Pierre VanderVegt | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *63-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *80-82* is/are allowed.

6)☒ Claim(s) *63-68,72-79 and 83-85* is/are rejected.

7)☒ Claim(s) *69-71* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08042004, 12102004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The Examiner in charge of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to F. Pierre VanderVegt, Ph.D. in Art Unit 1644.

Claims 1-62 have been canceled.

New claims 63-85 have been added and are the subject of examination in the present Office Action.

### *Response to Applicant's Summary of Informal Discussion*

1. As a first matter, Applicant apparently misunderstood the informal discussion with the Examiner. Accordingly, Applicant has misconstrued the substance of the discussion. The Examiner did not state that claims to antibodies or antibody fragments comprising CDR3 fragments of the disclosed monoclonal antibodies would be allowable. It should be noted that claims drawn to such an embodiment were present in the claim set previously under consideration and were rejected for the reasons of record in the Office Action mailed July 23, 2004.

What the Examiner actually indicated to the Applicant's representative in the informal discussion was that the disclosed deposited monoclonal antibodies or antigen-binding fragments thereof comprising the CDR3 region of the antibody would likely be allowable.

In view of Applicant's amendment and remarks filed November 26, 2004, the following grounds of rejection are maintained as they pertain to the claims filed November 26, 2004.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 63-68, 72-79 and 83-85 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

It was previously stated (with *emphasis* upon the segment particularly maintained): "Applicant's arguments filed April 24, 2004 have been fully considered but they are not persuasive. Applicant has submitted new claims to remove the recitation of "functional variants," reciting only that the claims include "conservative substitutions," asserting that the specification at page 19, line 23 through page 20, line 9 provides adequate support for demonstrating that Applicant had possession of the claimed invention. The examiner respectfully disagrees with applicant's position. It is noted that the specification at page 19, line 23 through page 20, line 9 defines "conservative substitutions" only in terms of an "amino acid substitution that does not alter the relative charge or size characteristics of the peptide in which the amino acid substitution is made" (page 19, lines 27-29, for example). Other than the assertion that conservative substitutions can be made to generate "functional equivalents," there is no evidence that the number of substitutions within a single CDR3 segment which can be tolerated without affecting the "function" of the CDR3 has been even contemplated. While a single substitution may not "alter the relative charge or size characteristics of the peptide," substitution of 50 or 60% of the amino acids in a single CDR3 is likely to affect those properties.

*Furthermore, the claims, reading upon any MBL-binding peptide comprising the CDR3 (or a variant comprising conservative substitutions therein) of one of the three recited monoclonal antibodies reads upon any antibody that may contain the same CDR3 (or a variant comprising conservative substitutions therein). This reads upon any other MBL-binding antibody molecule that possesses a CDR3 region meeting these limitations. The likelihood of other MBL-binding antibody clones using the same CDR3 or one with only conservative substitutions would be expected by one skilled in the art to be quite high because, being directed to the same antigen, as the same germline gene would be expected to generate multiple clones with variations due to hypermutation. However, the three monoclonal antibodies of the present specification do not provide an adequate amount of written descriptive support for this as-yet undetermined genus of anti-MBL antibodies.*

Lastly, Applicant does not appear to have been in possession of conservative substitutions of the CDR1, CDR2 or CDR3 regions of the described monoclonal antibodies because the sequence of the monoclonal antibodies is not disclosed. Accordingly, without knowing the sequence of the parent antibody, Applicant could not possibly have known of variants of those regions comprising conservative substitutions. The specification also does not disclose which residues of the core sequence are required for binding, i.e., cannot be changed and maintain functional MBL binding, nor does it disclose where within that core sequence amino acid residues can be added, which residues can be changed or deleted or what type of change can actually be tolerated. It does not appear based upon the limited disclosure that Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the limited number of species disclosed and the extensive variation permitted within the genus of i) a CDR3 of a monoclonal antibody produced by hybridoma cell line 3F8 deposited under ATCC Accession No. HB-12621, hybridoma cell line 2A9 deposited under ATCC Accession No. HB-12620, or hybridoma cell line hMBL1.2 deposited under ATCC Accession No. HB-12619, or

ii) a CDR3 of i) with a conservative substitution therein, wherein the conservatively substituted CDR3 binds to human MBL."

Applicant's arguments filed November 26, 2004 have been fully considered but they are not persuasive.

The new claims continue to read upon any MBL-binding peptide comprising the CDR3 of one of the three recited monoclonal antibodies reads upon any antibody that may contain the same CDR3. This reads upon any other MBL-binding antibody molecule that possesses a CDR3 region meeting these

limitations. The likelihood of other MBL-binding antibody clones using the same would be expected by one skilled in the art to be quite high because, being directed to the same antigen, as the same germline gene would be expected to generate multiple clones with variations due to hypermutation. However, the three monoclonal antibodies of the present specification do not provide an adequate amount of written descriptive support for this as-yet undetermined genus of anti-MBL antibodies.

Applicant argued "at least the deposit of the hybridomas that produce the antibodies from which the CDR sequences are obtained is adequate to demonstrate possession of the sequences for such CDRS." This is not disputed. However, Applicant's claims are drawn to antibodies comprising the CDRs and the CDRs in those antibodies are arranged in relation to one another by the intervening framework regions of those antibodies. Applicant's deposit demonstrates only possession of a single monoclonal antibody possessing the CDRs of monoclonal antibody 3F8, and that is the monoclonal antibody 3F8 produced by the hybridoma cell line deposited under ATCC Accession No. HB-12621. Applicant's deposit demonstrates only possession of a single monoclonal antibody possessing the CDRs of monoclonal antibody hMBL1.2, and that is the monoclonal antibody hMBL1.2 produced by the hybridoma cell line deposited under ATCC Accession No. HB-12619. Applicant's deposit demonstrates only possession of a single monoclonal antibody possessing the CDRs of monoclonal antibody 2A9, and that is the monoclonal antibody 2A9 produced by the hybridoma cell line deposited under ATCC Accession No. HB-12620.

3. Claims 63-68, 72-79 and 83-85 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody produced by the hybridoma cell lines 2A9, 3F8 and hMBL1.2 and antigen-binding fragments thereof does not reasonably provide enablement for the broader recitation of a peptide comprising an MBL CDR3 region of said antibodies, other antibodies bearing the same CDR3 or with a conservative substitution in the CDR3, CDR2 or CDR1 thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

It was previously stated: "Applicant traverses the rejection on the grounds that a working model is not needed, it would not require undue experimentation to show that a peptide consisting of one of the disclosed CDR3 peptides would bind to MBL, and applicant has shown that peptides such as the antibodies disclosed, F(ab) and $F(ab')_2$ fragments bind to MBL. Applicant's arguments are not persuasive. In the first case, while a peptide consisting of one of the disclosed CDR3 regions may very well bind to MBL, there is no adequate demonstation that longer peptides of, other than the CDR3 segment, undisclosed sequence will also bind to MBL. The amino acid residues which would flank the CDR3, while not directly involved with the act of binding will, nevertheless, affect the ability of that CDR3 to bind MBL, as each residue contributes to the overall 3D and charge characteristics of the

peptide. Applicant argues, in regard to the Janeway reference (of record), that CDR1 and CDR2 "might further contribute partially to binding," in asserting that Janeway stresses the importance of CDR3 to binding. In fact, Janeway treats CDR1, CDR2, and CDR3 equally and does not emphasize any one over the others. Further, Janeway clearly shows that not only are all three CDRs important, but the intervening sequences contribute significantly to the 3-dimensional relationship of CDR1, CDR2, and CDR3 to one another, orienting the CDRs properly for forming the binding site. Applicant's further contention that peptides comprising the CDR3, in the form of F(ab) and $F(ab')_2$ fragments, have been shown bind MBL is not convincing to support the broad recitation of the claims, as applicant is reminded that F(ab) and $F(ab')_2$ fragments also comprise CDR1 and CDR2 regions and comprise both the heavy chain variable region and the light chain variable region, meaning that the Ab fragments have CDR1, CDR2, and CDR3 contributions from both chains.

Applicant attempts to support the argument that peptides comprising the CRD3 would be able to bind MBL by citing articles by Laune, Monnet, Taub and Igarashi (citations on page 9 of response filed April 24, 2004). However, each of the references teaches that CDR-containing fragments of the antibodies from which they are derived are capable of binding to the target antigen. The references do not support conservative substitutions, nor do they support peptides not derived from the antibody comprising the CDRs.

Lastly, the specification is not enabling for the making of peptides comprising conservative substitutions of the CDR1, CDR2 or CDR3 regions of the described monoclonal antibodies because the sequence of the monoclonal antibodies is not disclosed. The specification also does not disclose which residues of the core sequence are required for binding, i.e., cannot be changed and maintain functional MBL binding, nor does it disclose where within that core sequence amino acid residues can be added, which residues can be changed or deleted or what type of conservative change can actually be tolerated. Without a teaching of even the sequence of the parent monoclonal antibodies, it would require an undue amount of experimentation on the part of the artisan to ascertain the sequences of the CDR1, CDR2 or CDR3 regions of the described monoclonal antibodies and make peptides with conservative substitutions therein, maintaining the ability to bind MBL."

Applicant argues that the ground of rejection is moot because of the cancellation of the previously pending claims and introduction of new claims. However, as stated in paragraph 1 *supra*, the "new" claims read upon the same embodiments as the claimed, accordingly the ground of rejection is maintained.

***Allowable Subject Matter***

4. Claims 80-82 are allowed.

5. Claims 69-71 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

*Conclusion*

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00; Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

F. Pierre VanderVegt, Ph.D.
Patent Examiner
February 15, 2005

PATRICK J. NOLAN, PH.D.
PRIMARY EXAMINER
2/17/05